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Short review

Interleukin-1, inflammasomes and the skin

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ABSTRACT

Interleukin (IL)-1 is a highly active and pleiotropic pro-inflammatory cytokine. Recent data impressively demonstrate that activating mutations in a human gene involved in proIL-1β maturation or loss-of-function mutations in the gene encoding IL-1 receptor antagonist (IL-1Ra) cause excessive activity of this cytokine. This can result in life-threatening systemic and local inflammation, particularly in the skin. Interestingly, experiments in mice revealed that epidermal keratinocytes can secrete large amounts of IL-1α, which induces an inflammatory response in the skin. Secretion of IL-1 requires caspase-1 activity, and activation of the protease takes place in innate immune complexes, called inflammasomes. As keratinocytes express and activate caspase-1 in an inflammasome-dependent manner, these epithelial cells might be critically involved in the innate immunity of the skin. In this review we summarize the current knowledge on IL-1 and inflammasomes in the skin, particularly their involvement in skin homeostasis and disease. In addition, we discuss the hypothesis that keratinocytes are not only static bricks of the epidermal wall, but immunologically active cells critically involved in different (auto)-inflammatory (skin) diseases.

Introduction

Inflammation represents a protective attempt by an organism to restore a new homeostatic state after its disturbance by a harmful stimulus. Depending on these stimuli the term inflammation is used for a broad range of conditions. For example, infections rapidly activate the innate immune system and induce an inflammatory response, which initiates the defence of the host against the invading pathogen. Tissue damage also results in local and acute inflammation, thereby allowing an efficient tissue repair response (Medzhitov, 2008). IL-1 plays an important role in these fundamental and beneficial processes (Dinarello, 2009a). However, inflammation can also be "undesired", chronic and destructive. It can contribute to major human diseases such as type 2 diabetes, atherosclerosis, asthma, Alzheimer's disease and cancer (Martinon et al., 2009). An involvement of IL-1 in the pathogenesis of these diseases has also been demonstrated. In particular, it is a leading actor in the recently defined auto-inflammatory diseases (Goldbach-Mansky and Kastner, 2009). These diseases are characterized by "sterile" inflammation without infection and the presence of autoantibodies or auto-reactive T cells. Reducing the activity of IL-1 results in rapid remission of symptoms (Aksentijevich et al., 2009; Goldbach-Mansky et al., 2006; Reddy et al., 2009). Interestingly, several auto-inflammatory diseases also affect the skin, and IL-1 activity plays an important role in inflammatory and allergic skin diseases such as psoriasis or contact dermatitis, demonstrating the importance of IL-1 in the skin (Goldbach-Mansky and Kastner, 2009; Numerof and Asadullah, 2006). Several lines of evidence suggest that keratinocytes are a major source of IL-1 in the skin (Feldmeyer et al., 2007; Lee et al., 2009; Szabowski et al., 2000). These non-professional immune cells represent the major cell type of the epidermis.

In this review we highlight the recent advances in the understanding of the role of IL-1 and inflammasomes in skin homeostasis and disease. In addition, we discuss a possible role of keratinocytes as sensors of danger and producers of IL-1.

The skin

In mammals, the skin consists of two layers, which are separated by the basement membrane (Fig. 1). The epidermis is the surface layer, a keratinized, stratified and squamous epithelium

Abbreviations: AIM, absent in melanoma; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CAPS, cryopyrin-associated periodic syndrome; CH, contact hypersensitivity; DAMPs, damage-associated molecular patterns; DC, dendritic cells; DIRA, deficiency in IL-1Ra; IL-1, interleukin-1; IL-1RI, IL-1 receptor type I; IL-1Ra, IL-1 receptor antagonist; LPS, lipopolysaccharide; LRR, leucine-rich repeat; MDP, muramyl dipeptide; NF-κB, nuclear factor κB; NLRP1, nucleotide-binding domain, leucine-rich repeat-containing receptor protein 1, also known as NALP1; PAMPs, pattern-associated molecular patterns; PRRs, pattern recognition receptors; ROS, reactive oxygen species; TNF, tumour necrosis factor; TLRs, Toll-like receptors; TNP, trinitrophenylchloride.

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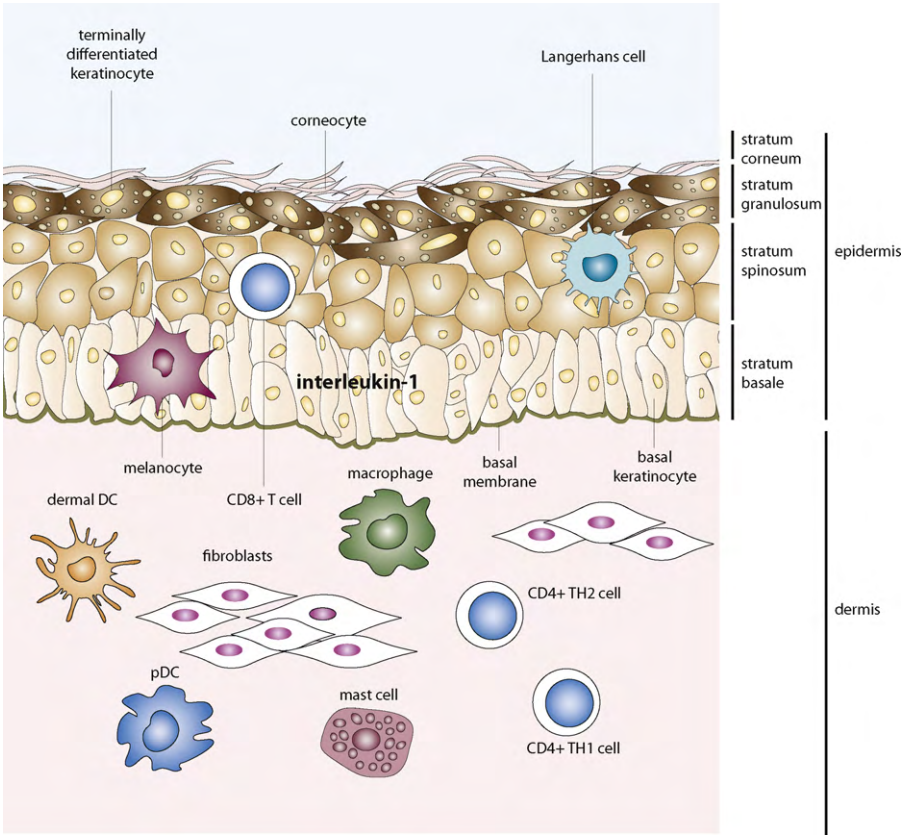

Fig. 1. The cellular composition of the skin. Keratinocytes are a major source of IL-1. When activated and secreted, the cytokine induces an inflammatory response through activation and recruitment of immune cells (inspired from Nestle et al., 2009a).

that is in permanent contact with the environment. The underlying dermis is a connective tissue composed of collagen, elastic fibres and a mixture of other extracellular matrix protein. It contains nerve endings, blood and lymphatic vessels, extracellular matrix-producing fibroblasts and several different types of immune cells such as macrophages, dendritic cells (DC), mast cells, and T cells (Nestle et al., 2009a). In contrast, the epidermis is made up almost exclusively of densely packed keratinocytes at different stages of differentiation. In addition, a few Langerhans cells, a type of DCs, and pigment-producing melanocytes can be found. The epidermis is in a constant equilibrium between proliferation of stem cells and transit-amplifying cells in the basal layer, and a terminal differentiation program of suprabasal keratinocytes (Fuchs and Raghavan, 2002). Keratinocyte terminal differentiation is an apoptosis-like process that generates dead, anucleated, flat and keratin-filled corneocytes in the *stratum corneum* at the surface of the epidermis, which are continuously replaced by new cells. The entire epidermis and in particular this layer of dead cells has an essential function as the first barrier against the environment.

The skin as an immune organ

Through its architecture and cellular composition the skin provides protection from injury and infection. The challenge for the largest organ of our body is to ensure efficient defence against pathogens and reliable immunosurveillance, but to avoid excessive immune responses, which might result in auto-immunity and chronic inflammation. The epidermis is in constant contact with multiple microbes (1 million/cm^2). The interaction between these microorganisms, which produce bacteriolytic enzymes, antibiotics and antifungal substances, and their competition for the colonization of the surface helps maintaining the skin's homeostasis. In addition, an antimicrobial lipid layer produced by sebocytes covers the skin surface. Keratinocytes are an important source of antimicrobial peptides. They are produced constitutively (e.g. lysozyme and psoriasin), or after infection/inflammation (e.g. human β-defensins and cathelicidin LL-37) (Glaser et al., 2005). Besides their antimicrobial activity, antimicrobial peptides such as LL-37 have a chemotactic role and modulate the immunological properties of DC and T cells (Nestle et al., 2009b). Lymphocytes, mainly T cells and B cells, and their receptors are responsible for the acquired immunity. The adaptive immune response allows to specifically recognize and remember "non-self" antigens of pathogens, and to mount a strong attack on these pathogens each time they are encountered. However, at the first time when the acquired immune system gets into contact with a new antigen, this mounting requires some days. In contrast, the innate immunity is less specific, but much faster. It relies on the recognition of highly conserved non-self pathogen-associated molecular patterns (PAMPs), and this recognition results for example in the expression of pro-inflammatory cytokines. These cytokines are able to activate and attract immune cells, which in turn attack the pathogens. PAMPs are recognized by Toll-like receptors (TLRs), also called pattern recognition receptors (PRRs), which are expressed by immune cells such as monocytes, macrophages, DCs and granulocytes, but also by keratinocytes. This indicates that they initiate a first line response to various pathogen-derived components (Creagh and O'Neill, 2006; Kollisch et al., 2005; Ting et al., 2006). Agonists of TLRs include bacterial lipopeptides, peptidoglycan and lipoteichoic acid (TLR2), double-stranded RNA (TLR3), lipopolysaccharides (LPS) (TLR4), flagellin (TLR5), imidazoquinoline and single-stranded RNA (TLR7 and TLR8), as well as CpG-containing DNA (TLR9) (McInturff et al., 2005).

Besides professional immune cells such as macrophages, neutrophils, dendritic cells and lymphocytes, keratinocytes have been